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Cíntia Helena de Cardal e França

Inter and intra observer variability in cervical measurement by ultrasound in the first and second trimester of pregnancy: does it matter?

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U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

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Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

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Inter and intra observer variability in cervical measurement by ultrasound in the first and second trimester of pregnancy: does it matter?

Assessment of cervical measurement variability in pregnancy

Cíntia Helena de Cardal e França

Abstract

OBJECTIVES: The aim of this study was to evaluate the inter and intra observer variability in the cervical length (CL) measurement by transvaginal ultrasound (TVU) in the 1st and 2nd trimesters of pregnancy. METHODS: 55 singleton pregnant women were evaluated in the 1st or 2nd routine ultrasound. Each patient was blindly evaluated by 3 of the 4 observers who performed three measurements each. RESULTS: In the first and second trimesters patients were evaluated at 12.3 weeks (mean) and 21.3 weeks (mean), respectively. The intra-class correlation coefficient (ICC) between observers in the first and second trimester was 0.76 and 0.72, respectively, and the ICC within observers was 0.889 and 0.899, respectively. In both trimesters, the main source of variance was the patient and the second source of variance was the interaction Patient x Observer (12.0% and 13.5%). The observer and measurement explained a small proportion of variance in both trimesters (1.4% and 0.4%, respectively in the first trimester, and 3.3% and 0%, respectively in the second trimester). The residual variance was 10.6% and 11.2%, and the standard error of measurement was 1.78mm and 1.82mm. CONCLUSIONS: TVU is a reliable and reproducible method to predict preterm birth both in the first and second trimesters.

Keywords

Cervical length– Inter observer variability – Intra observer variability– Preterm birth-Screening– Transvaginal ultrasound

Introduction

Preterm birth (PTB) affects about 15 million pregnancies worldwide, representing a major social and economic burden[1]. PTB is considered a major cause of perinatal morbidity and mortality and most of the damage and fatal cases happen in infants delivered before 34 weeks [2, 3].

Although improvements in prenatal and neonatal care have been made, preterm delivery rates were not meaningfully decreased [4] and therefore strategies for a successful screening of preterm birth need to be implemented [3]. Traditionally, obstetricians rely on clinical factors to assess a woman´s risk for PTB; however, more than half of all preterm births will occur in women without any previous risk factor[5, 6].

In the last 15 years, cervical length (CL) has been regarded as an auspicious screening tool [1, 5, 7]. Pioneering work from Heath *et al.*[8] and Iams *et al.*[9] demonstrated that transvaginal assessment of cervical length was an effective method for both the prediction and management of spontaneous preterm labour. Additionally, promising therapeutical interventions, like vaginal progesterone and pessary, are making their way in the successful reduction of preterm birth [10, 11].

So far, the literature support that the best time to estimate the PTB risk by this method is between 18 and 24 gestational weeks[2, 5]. More recently, the focus of interest is being shifted to the first trimester of pregnancy though the measurement of the true cervical length can pose more demanding technicalities before 14 weeks. [2]

TVU is until now an objective tool for measuring CL and it is considered the gold standard approach for assessing CL in pregnancy [7]. However, no data on the reproducibility of the technique in the first and second trimesters of pregnancy is available in the literature and therefore it is not known if putative dissimilarities between operators can modify the final PTB estimated risk. The aim of this study was to investigate the inter and intra observer variability in the cervical measurement by TVU in both trimesters of pregnancy.

Methods

The data of this prospective study was collected on 55 singleton pregnant women evaluated for the first or second trimester routine ultrasound in Hospital de S. João. Fifty five women were randomly chosen for this study from routine ultrasound examinations and signed the informed consent approved by the S. João Hospital Center Ethical Committee.

In each visit, either in the first trimester routine ultrasound performed between 11-13 weeks or in the second, between 20 and 23 weeks, we recorded sociodemographic factors, obstetric history and medical history. Sociodemographic factors included maternal age, education and occupation. Information on current and previous pregnancies was asked. Maternal weight and height were also recorded to calculate BMI and cervical or other medical pathologies were inquired to the patients.

In order to compare inter and intra observer variability, all doctors undertook the following procedures (Figure 1). First, women were asked to empty their bladder and were placed in the lithotomy position. Second, the vaginal transducer (Voluson E6 GE) was introduced towards the anterior lip, avoiding excessive pressure (because it can artificially increase the cervix length). The goal was to obtain a longitudinal view of the entire length of the cervical canal, in which could be observed the hyperechoic endocervical mucosa, the internal and external cervical os. The anterior and posterior cervical lips should have identical thickness and the magnification was increased so that half of the screen was occupied by the image. After that, callipers were used to measure in sequence the linear distance between the triangular area that is more echogenic in the external cervical os and a V-shaped notch in the internal cervical os (Figure 2). These steps were performed by four different doctors (TC, SBM, TR and NM) who performed three measurements each in three different pictures. Despite having four doctors only three made the measurements in each patient, being blinded for the findings of the other observers. The three doctors performed these procedures randomly.

Each examination was accomplished during 2-3 minutes. In all cases, the first measurement of the first operator was the one assumed as reference for the systematic screening made as a routine procedure.

Mixed effect models were used to estimate the variance and the respective overall Intraclass Correlation Coefficient´s (ICC´s), through Generalization Theory. The models considered the following factors patient, observer, measurement and the interaction between patient and observer. The dependent variable was cervical length.

We also estimated the intra observer variability (agreement within each observer) using the two-way mixed ICC for single measure for each observer and the inter observer

variability (agreement between each observer) using two-way random ICC for single measure for each measurement.

The Bland-Altman plot was estimated for each pair of observers using the first measurement only. Observer 3 was excluded from the Bland-Altman plot of the first trimester because he only evaluated 5 patients.

Results

Characteristics of the patients

Table 1 presents descriptive statistics about sociodemographic factors and obstetric history of the patients. For the entire cohort of 55 pregnant women the mean age at enrollment was 29 ± 5 years old. The rate of spontaneous pregnancies was 98%. The mean of the previous pregnancies number was 1.64 ± 0.73 and the mean of previous deliveries was 0.51 ± 0.57. The majority of the patients had no antecedents of previous PTB. The mean BMI was 25 ± 4 kg/m^2 and when considering BMI as a three-level categorical variable, based on the World Health Organization (WHO) weight classes, 51% were classified in the normal range, 31% were overweight and 18% were obese. In what concerns education, only 25% had Master Degree.

Table 2 refers to the distribution of the cervical length measurement by ultrasound according to observer, measurement and trimester. The lowest and highest values of cervical length measurements in the first trimester were 33.21mm and 36.00mm, respectively and in the second trimester, 32.90mm and 37.53mm, respectively.

First trimester

In the first trimester patients were evaluated at 12.3 weeks, ranging from 79 to 91 days.

Table 3 presents the components of variance of the estimated size. From the main effects, the main source of variance in the measurement was the patient (75.5%) and the second source of variance was the interaction Patient x Observer (12.0%). The observer and measurement explained a small proportion of variance (1.4% and 0.4%, respectively). The residual variance was 10.6% and the standard error of measurement was 1.78mm.

The overall intra-observer reliability was 0.889 ranging from 0.867 to 0.913 (Table 4).

Table 5 shows that the overall inter-measurement reliability was 0.76 ranging from 0.72 to 0.79.

The mean difference between observers ranged from -0.40 to 0.21mm and the limits of agreement (1.96 x SD) ranged from 6.59 to 8.46mm (figure 3).

Second trimester

In the second trimester patients were evaluated at 21.3 weeks ranging from 133 to 159 days.

As for the first trimester, table 3 presents the components of variance of the estimated size. Similarly to the first trimester, the main source of variance in the measurement was the patient (58.3%) and the second source of variance was the interaction Patient x Observer (20.0%). The observer and measurement explained a small proportion of variance (12.9% and 0%, respectively). The residual variance was 8.81% and the standard error of measurement was 1.90mm. After eliminating observer 3, the total

variance in the measurement due to patient increased to 72.0% and the interaction Patient x Observer decreased to 13.5%. Also in this case, the residual variance was 11.2% and the standard error of measurement was 1.82mm.

Table 4 shows that the overall intra-observer reliability was 0.899 ranging from 0.850 to 0.914.

Table 5 shows that the overall inter-measurement reliability was 0.58 ranging from 0.53 to 0.64. After eliminating observer 3 the overall inter-measurement reliability was 0.72 ranging from 0.66 to 0.79.

The mean difference between observers ranged from -4.1 to 5.59mm and the limits of agreement (1.96 x SD) ranged from 5.67 to 11.3mm (figure 4).

Discussion

Although TVU is considered the gold standard approach for assessing CL in pregnancy, no data about the reproducibility of this technique in the 1st versus 2nd trimesters are available in the literature. So, the aim of this study was to investigate inter and intra observer variability in the cervical measurement by TVU.

We found similarly high intraobserver reproducibility in both trimesters (0.889 in the first trimester and 0.899 in the second). Souka *et al.* [12] also demonstrated high ICCs for intraobserver variability in cervical length measurements conducted by two operators on first trimester (0.967 for operator 1 and 0.986 for operator 2), which is according with our results. Also, our findings are in good accordance with the paper from Valentin and Bergelin [13]. The intraclass correlation coefficient for cervical

length measurements was 0.93. The study was accomplished by two examiners in pregnant women in the second or third trimester, and three replicate measurements of cervical length were taken by each operator.

The limits of agreement of standard error of measurement in the first and second trimesters were 3.49 mm and 3.72 mm, respectively, and 3.56 mm when we eliminated observer 3. These findings were also similar to those found by Valentin and Bergelin [13].

Souka *et al.*[12] also demonstrated that the mean cervical lengths (33mm for transvaginal ultrasound at 11 to 14 weeks and 31mm for transvaginal sonography at 16 to 24 weeks) were similar to ours – 34.44 mm in the first trimester and 34.95 mm in the second trimester.

The overall inter-measurement reliability was higher in the first than in the second trimester – 0.76 (ranging from 0.72 to 0.79) against 0.58 (ranging from 0.53 to 0.64). However, when we eliminated observer 3, the overall inter-measurement reliability in the second trimester (0.72, ranging from 0.66 to 0.79) was similar to the first trimester. In both trimesters, the main source of variance in the measurement was the patient (75.5% in the first trimester and 58.3% in the second) which indicates that most of the variability in the measurement is due to systematic differences between patients. This indicates that observers were highly successful in discriminating different patients.

However, it is important to note that variable Observer, as a component of variance in the measurement, increased considerably in the second trimester (1.4% against 12.9%). Also the interaction Patient x Observer showed a significant increase in the transition

from the first to the second trimester – 12.0% against 20.0%, proving that some patients had systematically higher values when measured by a certain observer.

The residual variance in first trimester was 10.6% and 8.81% in first and second trimesters, respectively, that means that there is some error even after adjusting for all factors (patient, observer and measurement).

When analyzing Bland and Altman plots in the first trimester, the mean difference between observers was nearly 0 mm, that means that there was no bias between each pair of two observers [14]. The limits of agreement (1.96 x SD) ranged from 6.59 to 8.46 mm, this is the range within which 95% of the differences between two observers are likely to fall [14]. This is in good agreement with Valentin and Bergelin[13] that found a mean interobserver difference of 0.4 mm. The limits of agreement of this study were 10 mm, so our observers in the first trimester were more precise and effective. In the second trimester, the mean difference between observers ranged from -4.1 to 5.59 mm and the limits of agreement (1.96 x SD) ranged from 5.67 to 11.3 mm. In this scenario, our limits of agreement were similar to Valentin and Bergelin findings [13]. The discrepancy of our results about limits of agreement between the first and second trimesters could be explained by the influence of observer 3 that obtained higher cervical length measurements. When observer 3 was eliminated, some results described in Table 2 changed, and so there was not a considerable increase in the variable Observer as a component of variance (1.4% in first trimester against 3.3% in the second trimester) neither interaction Patient x Observer (12.0% against 13.5%) or residual variance (10.6% against 11.2%).

Although literature has not been supportive regarding the value of first trimester CL in the prediction of PTB, the overall inter-measurement reliability was similar in the first

and in the second trimester .Therefore, first trimester transvaginal measurement of CL could be a most effective tool to predict PTB earlier in pregnancy.

Also, the overall intra-observer reliability was higher than overall inter-measurement reliability in both trimesters.

This is in good agreement with recent trials that found a very effective contribution of first trimester screening for PTB [12, 15]. Souka *et al*. [12] found that women who would deliver preterm had a substantially shorter cervix from as early as the first trimester and that measurement of CL in that period could predict PTB. Furthermore, the authors demonstrated that the risk of delivering very early increases exponentially as the first trimester cervix becomes shorter. They also proposed that CL in the first trimester could be useful in predicting PTB and correlation of the first trimester cervical measurement with maternal characteristics, like maternal weight and height, history of cervical surgery and history of spontaneous PTB would be important to be taken into account when considering using first trimester CL as a screening tool [12]. An algorithm combining maternal characteristics and cervical length in the first trimester can identify about 55% of pregnancies resulting in delivery before 34 weeks, at a false-positive rate of 10%. The detection rate for delivery at 34–36 weeks was only 20% [15].

In conclusion, we have shown that TVU is a reliable and reproducible technique and therefore it can be used confidently as a screening tool to predict PTB. In fact this kind of method is a simple skill to learn for ultrasound operators undertaking routine ultrasound examination in pregnancy and the infrastructure and equipment needed for screening are readily available in most maternity units [16, 17].

The overall inter-measurement reliability was similar in the first and in the second trimester. Therefore, first trimester transvaginal measurement of CL could be adopted as an earlier screening tool as long as it can successfully identify women at high risk for PTB. Consequently, the implementation of preventive measures earlier in pregnancy could contribute to reduce PTB rates more effectively.

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Conflict of interest

None.

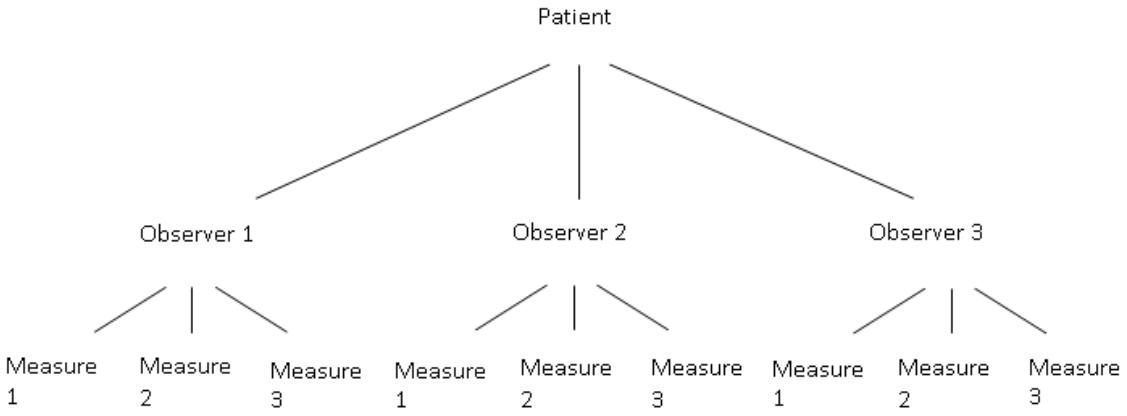

Figure 1- Method of evaluation of the 55 pregnant patients. Each patient was evaluated separately by 3 of the 4 observers

Figure 2- Ultrasound pictures illustrating the measurement of cervical length (distance between the external cervical os and internal cervical os) by the same observer

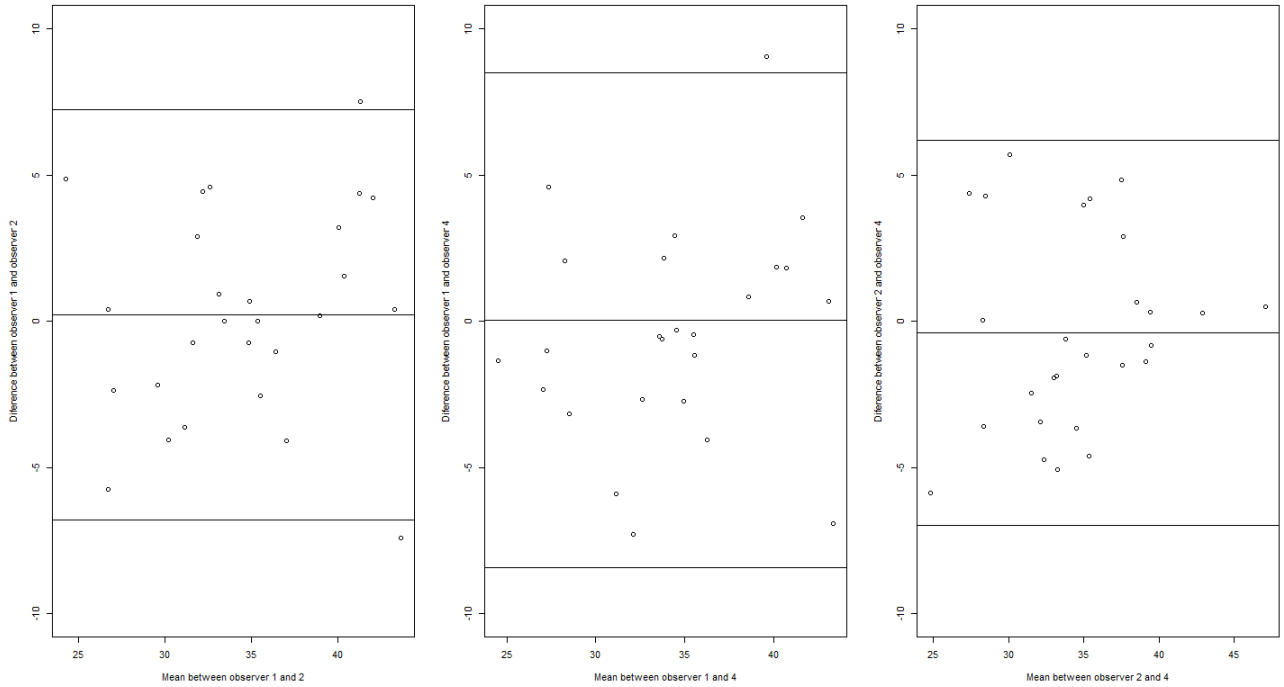

Figure 3- Bland-plots of difference for the 1st trimester between observers 1st measurement and the average of the two observers

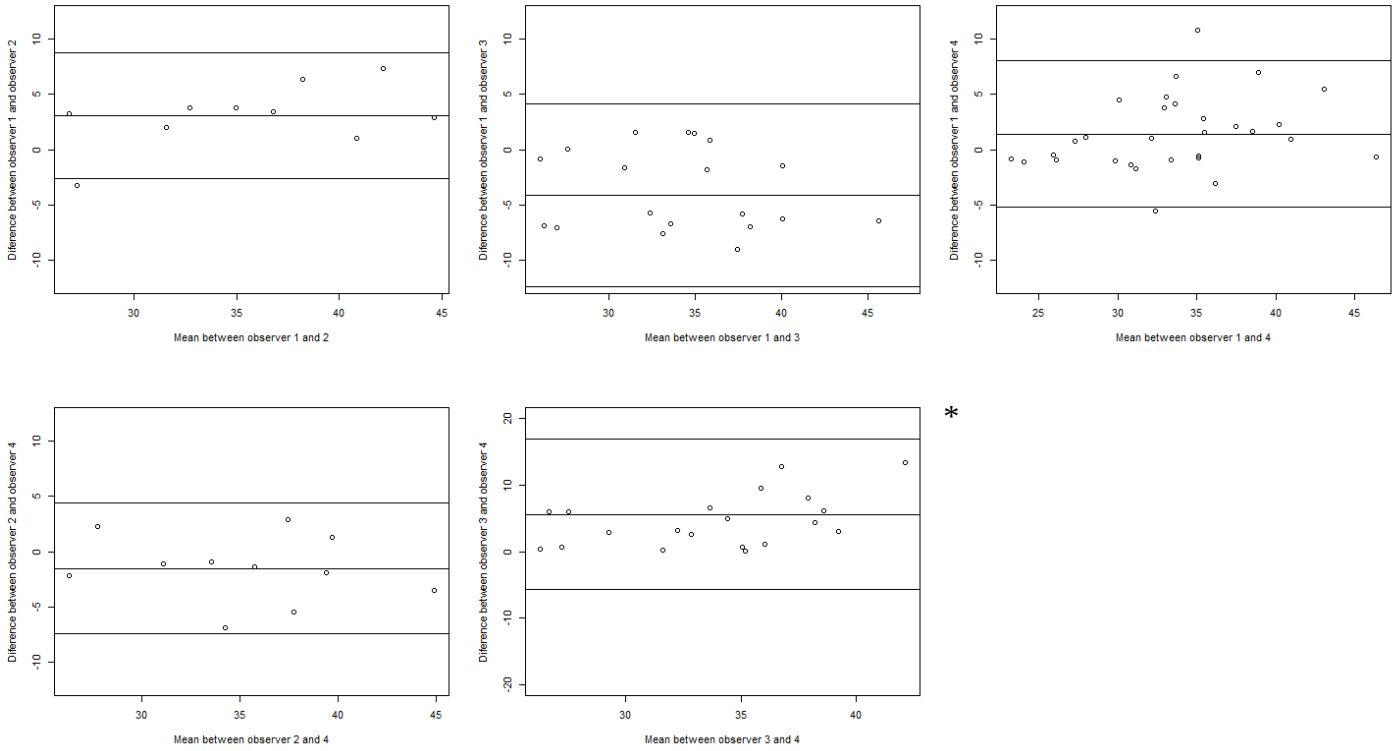

Figure 4- Bland-plots of difference for the 2nd trimester between observers 1st measurement and the average of the two observers. * In a different scale

Table 1. Descriptive statistics about sociodemographic factors and obstetric history (n=55)

Maternal Age (mean ± SD)	29 ± 5
Type of pregnancy n (%)	
Spontaneous	54 (98)
Induced	1 (2)
Previous pregnancies (mean ± SD)	1,64 ± 0,73
Previous deliveries (mean ± SD)	0,51 ± 0,57
Previous PTB n (%)	
No	54 (98)
Yes	1 (2)
BMI (mean ± SD)	25 ± 4
BMI category n (%)	
Normal (< 25 kg/m^2)	28 (51%)
Overweight (25-30 kg/m^2)	17 (31%)
Obese (>30 kg/m^2)	10 (18%)
Education n (%)	
4 - 9 years	18 (33)
10 - 12 years	20 (36)
> 12 years	14 (25)
Missing	3 (6)

Table 2. Distribution of the cervical measurement by ultrasound according to observer, measurement and trimester

	1st Trimester			2nd Trimester		
Measurement	1	2	3	1	2	3
Observer 1 (mean ± SD)	34.57±5.95	35.80±5.66	36.00±6.31	34.21±6.17	34.67±5.89	34.96±6.28
Observer 2 (mean ± SD)	34.34±5.28	34.07±5.54	34.22±4.99	34.51±5.42	35.26±3.73	34.92±4.61
Observer 3 (mean ± SD)	33.84±3.36	33.21±3.98	35.29±4.15	37.02±6.83	37.21±7.84	37.53±7.91
Observer 4 (mean ± SD)	34.33±5.28	33.92±5.16	33.75±5.09	32.91±5.19	33.28±5.03	32.90±4.67

Table 3. Random effects model to estimate components of variance in the measurement of first and second trimesters

	1st Trimester				2nd Trimester				2nd Trimester[2]			
	n	Var	SD	% of total variance[1]	n	Var	SD	% of total variance[1]	N	Var	SD	% of total variance[1]
Patient	30	22.47	4.74	75.5%	31	23.99	4.90	58.3%	31	21.30	4.62	72.0%
Observer	4	0.43	0.66	1.4%	4	5.31	2.30	12.9%	3	0.97	0.99	3.3%
Patient x Observer	90	3.56	1.88	12.0%	93	8.21	2.86	20.0%	72	3.99	2.00	13.5%
Measurement:(Observer)	12	0.14	0.37	0.4%	12	0.00	0.00	0.0%	9	0.00	0.00	0.0%
Residuals	270	3.15	1.78	10.6%	279	3.62	1.90	8.81%	216	3.30	1.82	11.2%

[1] Variance of each component divided by the total variance

[2] Analysis without observer 3

Table 4. Agreement within each observer in the first and second trimesters

	1st Trimester		2nd Trimester	
	n	ICC[1]	n	ICC[1]
Observer 1	28	0.867	30	0.912
Observer 2	29	0.913	11	0.891
Observer 3	5	0.895	21	0.914
Observer 4	28	0.906	31	0.850
Overall Agreement		0.889		0.899

[1] Two-way mixed ICC for single measure

Table 5. Agreement between each observer in the first and second trimesters

	1st Trimester	**2nd Trimester**	**2nd Trimester**[2]
	ICC[1]	ICC[1]	ICC[1]
Measurement 1	0.77	0.64	0.79
Measurement 2	0.79	0.58	0.70
Measurement 3	0.72	0.53	0.66
Overall Agreement	0.76	0.58	0.72

[1] Two-way random ICC for single measure; [2] Two-way random ICC for single measure without observer 3

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ANEXOS

Journal of Perinatal Medicine: Instructions for Authors

Scope of the journal

- ***Journal of Perinatal Medicine*** publishes original papers and reviews on all aspects of obstetrical and neonatal research and provides rapid publication for all items of articles:
- **Review articles** providing a coverage of theoretical and practical points of view in a particular field: Manuscript: length according to previous arrangement. References should be limited to max. 50 citations.
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2. *Organization as author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension. 2002;40:679–86.

3. *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325:184.

4. *Book: Personal author:*

Carlson BM. Human embryology and developmental biology. 3rd ed. St. Louis: Mosby; 2004.

Brown AM, Stubbs DW, editors. Medical physiology. New York: Wiley; 1983.

5. *Chapter in a book:*

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93–113.